APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,659	07/09/2003	Costas D. Maranas	P06367US03	9959

			EXAMINER
27407	7590	09/19/2006	SKOWRONEK, KARLHEINZ R

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ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 09/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *07 April 2006*.

2a) ☐ This action is **FINAL**.   2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-20* is/are pending in the application.

   4a) Of the above claim(s) *6,9 and 15-17* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 7-8, 10-14, and 18-20* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

   Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

   Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   a) ☐ All   b) ☐ Some * c) ☐ None of:

   1. ☐ Certified copies of the priority documents have been received.

   2. ☐ Certified copies of the priority documents have been received in Application No. _____.

   3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

   * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *(6 sheets)*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Applicant's election without traverse of species of group A directed to the growth

objective (cl. 5 and 14), group B directed to lactate engineering (cl. 18) and group C

directed to bilevel optimization (cl. 8) in the reply filed on 07 April 2006 is acknowledged.

Claim 20 is new.

Claims 1-20 are pending.

Claims 6, 9, and 15-17 are withdrawn from consideration as directed to non-elected

species.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e)

or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied

with one or more conditions for receiving the benefit of an earlier filing date under 35

U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention

which is also disclosed in the prior application (the parent or original non-provisional

application or provisional application). The disclosure of the invention in the parent

application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v.*

Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/395,763, fails to

provide adequate support or enablement in the manner provided by the first paragraph

of 35 U.S.C. 112 for one or more claims of this application. Accordingly, Claims 1-14

and 18-20 are not entitle to the benefit of the prior application

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 10/28/2004,

08/05/2004, and 07/09/2003 consisting of 6 sheets were filed before the mailing of the

first action on the merits. The submission is in compliance with the provisions of 37

CFR 1.97. Accordingly, the examiner has considered the information disclosure

statements.

Claim Rejections - 35 USC § 112, Second Paragraph

1.   Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite

for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention.

In the instant case, claim 2 is drawn to the modifying an organism with the

candidate. It is unclear what is being modified, the model of the organism or the

organism itself. Further, it is unclear what the modification is. Is the modification

genetic/physical or is it abstract?

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of
making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the formation of a bilevel optimization problem, does not reasonably provide enablement for the formation of any optimization problem. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors

are considered, a sufficient amount for a *prima facie* case is discussed below.

Claim 1 is dawn to a method using a model of an organism's metabolic pathways

to determine potential genes which could be modified by deletion or addition in order to

obtain a desired product or effect via the steps: selecting a bioengineering objective;

selecting at least a cellular objective; and forming an optimization problem.

Breadth:

The breadth of the claim is so wide as to encompass any model of any organism,

multiple cellular objectives, any bioengineering objective, and forming and solving any

optimization problem.

Nature:

The nature of the invention relies on a model of a metabolic network and the

algorithm capable of describing/forming any optimization problem, the calculations

performed and selection/decisions required to predict the candidate genes in the

metabolic network.

State of the Art:

The state of the art at the time of invention had been applying the statements of

mathematics, such as Linear Programming optimization problems (cf. Schilling et al,

Biotechnology and Bioengineering, 71(4):286-306, 2001) and algebraic optimization

problems, to the analysis and modeling of metabolic networks to predict the

"phenotypes" of alterations to the reaction steps that make up a metabolic pathway for a

particular organism. The optimization problems have been analyzed with various

computational environments, such as MATLAB (cf. Klamt et al., Bioinformatics,

19(2):261-269, 2003). However, the formation of an optimization problem and

concomitant mathematical statement and solution of the problem presents a complex,

computational hurdle that remains to be overcome. Methods, such as network division

or metabolite grouping have be practiced to reduce the computational complexity of the

optimization problems, but these methods introduce other issues, like the overlaps

between many metabolite biosynthetic pathways (Papin et al., 5/2003, Trends in

Biochemical Sciences, 28(5):250-258, p.256, "computational obstacles").

Lack of guidance:

The specification provides guidance for the formation of a bilevel optimization

problem. However, the specification does not provide guidance for forming any

optimization problem. The specification does not specifically define "optimization

problem". Giving the term "optimization problem" its broadest meaning, it is interpreted

to mean any method that results in attaining a biological objective and a cellular

objective. The specification also provides no examples of the formation of other

optimization problems.

Level of ordinary skill:

One of ordinary skill in the art would be able to make the invention that practices

a limited number of known optimization problems. However the breadth of claim is such

that optimization problems that have not been conceived or novel are also included.

One of ordinary skill in the art would not be able to make the invention without undue

experimentation which is required to conceive and develop a novel optimization

problem.

Thus undue experimentation would be required for one of ordinary skill in the art

to make or use the invention within the full scope of claims.

Claim Rejections - 35 USC § 103

2.   Claims 1-5, 7-8, 10-14, and 18-20 rejected under 35 U.S.C. 103(a) as being

unpatentable over Burgard et al. (Biotechnology and Bioengineering. 2001 74:364-375),

in view of Yang et al. (metabolic engineering, 1999, 1:26-34) and further in view of Voit

(Biotechnology and Bioengineering, 1992, 40: 572-582).

To the extent of the elected species, claims 1-5, 7-8, 10-14, and 18-20 are drawn

a method of identifying gene candidates for deletion and addition by forming and solving

a bilevel optimization problem that involves a bioengineering objective, e.g. lactate

overproduction and a cellular objective, e.g. maximizing growth in an organism.

Burgard et al. teach a method of identifying gene candidates for deletion and

addition by forming and solving an optimization problem that involves a bioengineering

objective and a cellular objective ("Mathematical modeling of gene additions/deletions",

p367-369).

Burgard et al. do not teach the generation of a bilevel optimization problem; also

the reference does not teach lactate overproduction as a "bioengineering objective".

Yang et al. teach lactate overproduction in E. coli by the deletion of the

phosphotransacetylase gene, PTA, and the acetate kinase gene, ackA. Yang et al also

demonstrate the underproduction and overproduction of chemicals, specifically acetate

and lactate, relative to the wild type strain. One of ordinary skill in the art will also

recognize lactate as a carbon source used in by E. coli during anaerobic fermentation.

Voit teaches the application of bilevel programming optimization ("multilevel

programming", p.572), techniques as S-system, to bioengineering of organism strains

("design of pathways", p. 579) by solving the optimization problem to identify candidates

for deletion and addition ("to optimize a yield", p.573 and p.576).

It would have been obvious to one of ordinary skill in the art at the time the

invention was made to use the bilevel optimization of Voit in the method of Burgard et

al. to develop the strain of E. coli that overproduce lactate as taught by Yang et al. One

would have been motivated to combine the teachings of Burgard et al., Yang et al and

Voit to result in the instantly claimed invention, by Yang et al. because the organism, E.

coli, is " extensively used in industry as a host for recombinant protein production (Yang

et al, p. 26-27)" and by Voit because bacteria could be used to produce unnaturally high

amounts of oxychemicals that can be used as alternative fuels (p. 579)" and

recombinant protein production and would have reasonably expected success in view of

the teachings of Burgard et al and Voit. Accordingly the invention as a whole is *prima*

facie obvious.

With respect to the limitations of claim 2, drawn to modifying an organism with a

candidate, is also taught by Yang et al. in which the *pta* gene of E. coli was knocked out

to generate a *pta* deficient organism (see table 2a, p. 27, Yang et al.).

With respect to the limitation of claim 7, drawn to a candidate deletion and a binary value specifying if a reaction is active or inactive, is also taught by Burgard et al. Burgard et al. teach the use of a binary value to specify if a reaction is active or inactive, "the binary parameter, a_{jk}, is defined to describe which enzymes are coded for by which genes: $a_{jk} = 0$ if gene k has no direct effect on reaction j; 1 if gene k codes for an enzyme catalyzing reaction j ("binary parameter", p367-368, Burgard et al.). This reads on the limitation of claim, the assignment of a binary value to a reaction flux. The limitation of deletions is taught in, "In this study we explore what is the smallest gene set capable of maximizing biomass production on glucose substrate (uptake 10mmol) and what is the maximum number of gene deletions from this gene set that still maintains a specified level of biomass production (p.369)".

The above statement also teaches the limitations of claim 13 drawn to the evaluation of performance limits ("smallest gene set"), the limitations of claim 20 and 14, drawn to an objective corresponding to maximizing growth rate, and the limitations of claim 5, drawn to growth ("maximizing biomass production"). The title of Burgard et al. also reads on the limitations of claim 13, performance limits.

With respect to the limitations of claim 11, drawn to a chemical uptake constraint, is also taught by Burgard et al., "quantifies the network's uptake (if negative) or secretion (if positive) of metabolite i. (p. 366)" and "stoichiometric coefficient of metabolite i (p.366)". Metabolites are known in the art to chemical in nature and stoichiometric coefficient is a constraint.

With respect to the limitation of claim 12, drawn to quantifying the cellular objective as an aggregate flux, is also taught by Burgard et al. as "maximized the biomass production $\underline{flux}$, $v_{max\,biomass}$. The solution yields the maximum theoretical level of biomass production ($v_{max\,biomass}$ = 1.25g biomass/gDW·h) achievable by the metabolic network within the stoichiometric constraints (p. 369)".

With respect to the limitation of claim 10, drawn to at least one stoichiometric, is also taught by Burgard et al. in "These upper bounds are set by maximizing the given flux n_j subject to the stoichiometric constraints (p. 369)".

With respect to the limitations of claim 19 are intrinsic to the teaching of Burgard et al., "These problems are solved using CPLEX 6.6 accessed via the commercial software package GAMS. Problems with up to 3700 binary variables were solved on an IBM RS6000-270 workstation (p. 369)".

Provisional Double Patenting, 35 USC § 101

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain $\underline{a}$ patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

3.   Claim 19 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-18 of copending Application No. 10/929,091. Claims 1-18 of copending Application No. 10/929,091 are drawn to a computer assisted method for identifying gene additions that incorporates the use of a bilevel optimization problem, selecting bioengineering and cellular objectives. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

        No claims are allowed.

        Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karlheinz R. Skowronek whose telephone number is (571) 272-9047. The examiner can normally be reached on Mon-Fri 8:00am-5:00pm (EST).

        If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information

system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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